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Ovarian cancer

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Abstract

Ovarian cancer is not a single disease and can be subdivided into at least five different

histological subtypes that have different identifiable risk factors, cells of origin, molecular compositions, clinical features and treatments. Ovarian cancer is a global problem, is typically diagnosed at late stage, and has no effective screening strategy. Standard treatments for newly diagnosed cancer consist of cytoreductive surgery and platinum-based chemotherapy. In recurrent cancer, chemotherapy, anti-angiogenic agents, and poly (ADP ribose) polymerase (PARP) inhibitors are used and immunological therapies are currently being tested. High-grade serous carcinoma (HGSC) is the most commonly diagnosed form of ovarian cancer and is typically very responsive to platinum-based chemotherapy at diagnosis. However, in addition to the other histologies, HGSCs frequently relapse and become increasingly resistant to chemotherapy. Consequently, understanding the mechanisms underlying platinum resistance and finding ways to overcome them are active areas of study in ovarian cancer. Significant progress has been made in identifying genes associated with high risk of ovarian cancer (such as *BRCA1* and *BRCA2*) as well as a precursor lesion of HGSC called a serous tubal intraepithelial carcinoma, which hold promise for identifying individuals at high risk of developing the disease and for developing prevention strategies.

Competing interests

U.A.M. has served as a consultant for AstraZeneca, ImmunoGen, Pfizer, Genentech, and Merck.

A.K.S., L.F., B.E.H., J.S. and B.Y.K. declare no competing interests.

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[H1] Introduction

Although once considered a single entity, ovarian cancer can be subdivided into different histological subtypes that have different identifiable risk factors, cells of origin, molecular compositions, clinical features and treatments. These histological subtypes include epithelial cancers which account for ~90% of ovarian cancers and include serous, endometrioid, clear cell and mucinous carcinomas (Figure 1, Table 1). Of these types, high grade serous carcinoma (HGSC) is the most commonly diagnosed. Histologically and clinically, low-grade endometrioid and low serous carcinomas are different compared to their high-grade counterparts; HGSC is similar to high-grade endometrioid carcinomas (98, 100, 101). Other rarer histologies include small cell carcinoma (aggressive cancers that predominantly occur in younger women with a median age at diagnosis of 25 years of age) which have an uncertain tissue origin and carcinosarcoma (also an aggressive cancer) (1, 2). Non-epithelial ovarian cancers, including germ cell tumours and sex cord stromal tumors which account for approximately 10% of ovarian cancers are not discussed in this Primer.

Some ovarian cancers originate from sites outside of the ovary; for example, many ovarian HGSCs likely originate in the fallopian tube (3) and some subsets of ovarian cancer have been shown to arise from the peritoneum (ref). Also, clear cell and endometrioid carcinomas can originate from endometrial tissue located outside the uterus (endometriosis). On the basis of new WHO classification, most of these types of ovarian cancer will now be reclassified as ‘ovarian or

tubal cancers' (4). Indeed, information regarding precursor sites of ovarian cancer has enabled the investigation of new primary prevention strategies, such as risk-reducing and opportunistic salpingectomy (surgical removal of the fallopian tube) (3). This increased understanding of the biology underlying ovarian cancer has also translated to changes in clinical research; clinical trials are now increasingly focusing eligibility requirements on the basis of ovarian cancer histology.

Effective screening strategies for the early detection of ovarian cancer do not exist, but individuals at high-risk of developing ovarian cancer, such as those with germline mutations in *BRCA1* or *BRCA2* (encoding proteins involved in the repair of DNA damage via homologous recombination) or other genes associated with high-risk of ovarian cancer, can be identified. For these individuals, strategies to reduce ovarian cancer risk have been implemented through risk-reducing surgery such as bilateral salpingo-oophorectomy (removal of the ovaries and fallopian tubes). Screening strategies in women with average risk of developing ovarian cancer have primarily focused on the biomarker CA125 (also known as mucin 16) and the use of transvaginal ultrasonography. Combinations of these screening modalities have shown success in detecting early stage cancers, but have not yet demonstrated definitive improvements in patient mortality (6, 7).

The most active therapeutic agents against newly diagnosed ovarian cancer are platinum analogues (either cisplatin or carboplatin), with the addition of a taxane (either paclitaxel or docetaxel) (8-12). Treatment paradigms for first-line management of newly diagnosed ovarian cancer include either primary surgical cytoreduction (to debulk tumours) followed by combination platinum-based chemotherapy or neoadjuvant chemotherapy (NACT, administering chemotherapy before surgery) followed by interval surgical cytoreduction and additional chemotherapy after surgery. Recurrence of cancer after initial platinum-based chemotherapy is

very common for women diagnosed with advanced cancer; is v the most difficult issue in the treatment of cancer in these women is the eventual development of platinum resistance. Advances in new therapeutics for recurrent ovarian cancer treatment include angiogenesis inhibitors, poly (ADP ribose) polymerase (PARP) inhibitors (which block the repair of DNA damage) and immunotherapy agents. Strategies using PARP inhibitors as part of the first-line treatment, as well as combinations of these therapies for the treatment of both newly diagnosed and recurrent ovarian cancer are underway. Overall, the treatment of ovarian cancer based on distinct genomic makeup of the individual histological subtypes of ovarian cancer is evolving.

This Primer reviews the epidemiology and known risk factors associated with epithelial ovarian cancer, in addition to the molecular biology, diagnostic and prevention approaches and management of both newly diagnosed and recurrent cancer. This Primer also discusses patient quality of life and concludes with examination of the future outlook for ovarian cancer, including new prevention and screening approaches and promising new therapeutic advances.

[H1] Epidemiology

[H2] Incidence and mortality

Globally, 225,500 new cases of ovarian cancer are diagnosed each year, with 140,200 cancer-specific deaths (13-15). Incidence and survival rates vary by country; Russian and the United Kingdom have the highest worldwide rates while China has the lowest rates of ovarian cancer (ref) . In the United States, approximately 22,280 new cases occur annually and the projected number of deaths is 14,240 for 2016 (13). Interestingly, the annual incidence of ovarian cancer reduced by 1.09% for women < 65 years of age and by 0.95% for women ≥ 65 years between 1998 and 2008 (ref), which might have been influenced by the changing pattern of hormonal therapy prescriptions; reduced risk of ovarian cancer coincided with the announcement of causal

association between ovarian cancer and use of hormonal replacement therapy and as such, fewer prescriptions were written (37).

Over the past decade, minimal improvement in mortality has been observed (14, 15). The US Surveillance, Epidemiology, and End Results database reports that overall survival for all patients with ovarian cancer is 45.6%, but this varies greatly based on stage at initial diagnosis (16); 5-year overall survival in patients with stage I cancer is 92.1% but is 25% for patients with stage III and IV cancer (13, 16).

[H2] Risk factors

Several factors can increase the risk of developing ovarian cancer, including genetic factors, age, post-menopausal hormonal therapy use, infertility and nulliparity.

[H3]Genetics. A range of genetic factors are associated with an increased risk of developing ovarian cancer (Table 2). Germline *BRCA1* and germline *BRCA2* mutations are the most significant known genetic risk factors for ovarian cancer and either mutation is found in up to 17% of patients (70, 71). Moreover, mutations in *BRCA* increases the risk of other cancers, such as breast cancer, pancreatic cancer, prostate cancer and melanoma (*BRCA2 only*) and inheritance of these genes have been extensively studied (17-19). Most subtypes of epithelial ovarian cancer are associated with germline *BRCA* mutations, but HGSCs are the most common (17, 18) and mucinous subtypes are rarely associated. Survival is improved for women with ovarian cancer carrying germline *BRCA* mutations, compared with women who have ovarian cancer but are wild-type for *BRCA1* and *BRCA2* (19). Germline *BRCA2* mutations are associated with increased overall survival, compared with germline *BRCA1* mutations, likely because *BRCA2* results in enhanced platinum sensitivity and thus greater cancer cell killing compared with *BRCA1* (19, 20). Both the location of the *BRCA* mutation within the gene and the type of the mutation might also

influence risk of developing ovarian cancer; the risk of developing breast cancer or ovarian cancer, as well as the median age at diagnosis, can vary according to mutation type, nucleotide position and the functional consequence of the mutation in patients with germline *BRCA1* or *BRCA2* mutations (21).

Besides *BRCA1* and *BRCA2*, other germline mutations in genes involved in DNA repair can increase the risk of developing ovarian cancer, including genes that are part of the Fanconi anaemia/BRCA pathway, such as *RAD51C*, *RAD51D*, *BRIP1*, *BARD1*, and *PALB2* (18, 22-25; Table 2). Inherited mutations in other genes involved in DNA repair, such as *CHEK2*, *MRE11A*, *RAD50*, *ATM* and *TP53*, might also increase the risk of developing ovarian cancer (18, 22, 23).

Other inherited disorders, such as Lynch syndrome, can increase the risk of ovarian cancer. Lynch syndrome is associated with colorectal, endometrial and ovarian cancers, but can also be associated with cancers of the urinary tract, stomach, small intestine and biliary tract. The syndrome is characterized by inheritance of a germline mutation in genes of the DNA mismatch repair system, namely, *MLH1*, *PMS2*, *MSH2*, or *MSH6*, which are mutated in differing frequencies (26-28). Patients with Lynch syndrome-associated ovarian cancer have a mean age at presentation of 48 years (compared with a median age of ~68 years in those without Lynch syndrome), with approximately 50% of patients having stage I cancer. Additionally, endometrioid and clear cell carcinomas are more common in patients with Lynch syndrome than would be predicted for sporadic ovarian cancer (26). Even though both BRCA and the DNA mismatch repair pathways are involved in DNA repair, the specific mechanisms are not known why cancers arise in specific organs associated with these inherited mutated genes.

[H3] Oral contraceptives and hormone replacement therapy. The use of oral contraceptives has been shown to reduce the risk of developing ovarian cancer in individuals with a germline

BRCA1 mutation, as well as in those without a genetic predisposition (30, 31). One meta-analysis showed a lifetime reduction of 0.54% of ovarian cancer with the use of oral contraceptives for an average of 5 years (31) (ref). Interestingly, an analysis from the Ovarian Cancer Cohort Consortium (including data from 21 studies, encompassing 1.3 million women and 5,584 ovarian cancers) showed that oral contraceptive use was associated with reduction in serous, endometrioid and clear cell carcinomas, but not mucinous carcinomas (ref). The relative oestrogen and progestin doses in oral contraceptives does not affect the incidence of ovarian cancer, but longer duration of oral contraceptive use is associated with reduced risk (32). However, other meta-analyses have found insufficient evidence to recommend either for or against the use of oral contraceptives to prevent ovarian cancer, given their potential harm from adverse vascular events and minimal increase in other cancers (such as breast cancer) weighed against the potential for ovarian cancer risk reduction (32).

Hormone replacement therapy has been shown to increase the risk of developing ovarian cancer in post-menopausal women; oestrogen-only therapy increased risk by 22% and the combined oestrogen and progesterone therapy increased risk by 10% (33-35). However, a meta-analysis showed a similar increase in the risk of developing ovarian cancer, specifically, serous and endometrioid carcinomas, in menopausal women using hormone replacement therapy, regardless of whether the therapy contained only oestrogen or a combination of oestrogen and progesterone (36). Others have confirmed this finding but have also shown a reduced risk of clear cell cancer in women using hormone replacement therapy (Wentzensen et al JCO 2016). Interestingly, in women diagnosed with ovarian cancer and who also have severe menopausal symptoms, the use of hormone replacement therapy appears safe and has no effect on overall survival (38). Thus, use of hormone replacement therapy can be considered if patients are having significant menopausal symptoms (38).

[H3] Reproductive factors. Retrospective studies have identified several other factors that can influence the risk of ovarian cancer such as parity, prior tubal ligation, salpingectomy and unilateral or bilateral oophorectomy (surgical removal of the ovary) (29, 42,43). Women who have given birth have a reduced risk of all subtypes of ovarian cancer, with the strongest risk reduction noted for clear cell cancers, compared with women who have not given birth. Unilateral oophorectomy is associated with a 30% reduction in the risk of ovarian cancer, which is not histological subtype-specific. Bilateral oophorectomy is also effective in reducing risk of ovarian cancer in women with a genetic predisposition . Interestingly, 0% of women with a *BRCA2* mutation and 1.1% with a *BRCA1* mutation developed a primary peritoneal carcinoma following bilateral oophorectomy (ref). (42). Tubal ligation and hysterectomy are also associated with a reduction in the risk of developing ovarian cancer; tubal ligation is associated with reduction in risk of clear cell and endometrioid carcinomas and hysterectomy is associated with reduction in risk of clear cell carcinoma (Wentzensen et al) (29, 42, 43). In one study, reproductive risk factors such as tubal ligation, parity of ≥ 2 , endometriosis and younger age were more strongly associated with development of dominant ovarian tumors (meaning one ovarian tumour is at least twice as large as the tumour on the other ovary), than with non-dominant cancers which are thought to arise in the fallopian tube and are mostly HGSC (44). Also, endometriosis has been associated with endometrioid and clear cell ovarian cancer as well as low grade cancers (Wentzensen et al). In women with germline *BRCA* mutations, tubal ligation and breastfeeding have similarly been identified as a risk factor associated with a decreased risk of ovarian cancer (29).

[H3] Lifestyle factors. Several studies have identified obesity as a possible risk factor for the development of postmenopausal ovarian cancer; one meta-analysis showed an approximate 13% increase in risk of ovarian cancer in postmenopausal women with a 5kg weight gain, who did not use, or had low use of hormone replacement therapy (45). Moreover, obesity is associated with an elevated risk of endometrioid and mucinous carcinomas but not HGSC (ref). However,

conflicting data have been reported in other studies (Wentzensen et al). Obesity is also a risk for poor outcomes following diagnosis of ovarian cancer; women with obesity and low grade serous carcinoma (LGSC), HGSC or endometrioid carcinoma have a worse outcome compared with non-obese women (47). Meta-analyses have suggested a beneficial effect of regular physical activity on the risk of ovarian cancer, with a 30–60% reduction in risk in the most active women (46).

Several studies have examined the association between dietary factors and the risk of developing ovarian cancer in the general population. Levels of milk consumption do not confer a significant risk for developing ovarian cancer, but one study noted a trend suggesting an inverse association between intake of skim milk and lactose in adulthood and risk (49). Moreover, this study showed an inverse relationship between lactose intake and the risk of endometrioid carcinoma (49).

Studies have also assessed the association between other dietary factors, including vitamins and flavonoids and risk of ovarian cancer. The intake of folate or vitamins A, C, or E during adulthood, or intake of a specific diet (defined by dietary scores) does not alter the risk of ovarian cancer (53, 54). Interestingly, flavonoids and black tea might be associated with a reduced risk of ovarian cancer, but these require further study (55).

Other lifestyle factors that might affect the risk of ovarian cancer include the use of talc powder (reviewed in 52), medications such as NSAIDs and smoking. With respect to talc powder, results from case control and prospective studies have been variable; one study showed a modest increase in the risk of ovarian cancer, but other studies have shown no increase in risk with talc use (50, 51). Aspirin use was associated with a reduced risk of developing ovarian cancer, especially among women who took daily, low-dose aspirin, regardless of their age; the same associations were not shown for acetaminophen (56). Regular aspirin use was associated with

reduced risks of endometrioid and mucinous carcinomas and a significance reduction in risk of serous carcinomas. However, no prospective trials testing aspirin for ovarian cancer risk reduction have been conducted. Non-aspirin NSAID use was associated with a trend to suggest a lower risk of ovarian cancer (56), specifically, of serous carcinomas. Cigarette smoking was associated with a significantly lower risk of clear cell carcinoma but an increased risk of mucinous carcinoma (Wentzensen et al).

Finally, data from the Nurse's Health Study show that persistent depression – defined as meeting the definition of depression based on current and past questionnaires – might increase the risk of ovarian cancer compared with women who do not exhibit depressive symptoms (48)

[H1]Mechanisms/pathophysiology

The Cancer Genome Atlas (TCGA) project, along with other projects that catalogue genetic mutations associated with cancer have produced important molecular data of the different histological subtypes of epithelial ovarian cancer (63, 65, 66). These data, in turn, open the pathway to improved therapeutic, early detection and risk-reducing strategies. The recognition that ovarian cancer is comprised of histologically and molecularly distinct subtypes has influenced clinical trial design strategies and patient eligibility and has led to rational clinical management (Table 2) (67, 68).

[H2] Molecular alterations

The best-studied genetic alterations in ovarian cancers are those involved in DNA repair (Figure 3). Germline or somatic mutations in homologous recombination genes have been identified in approximately one third of ovarian carcinomas, including both serous and non-serous histologies

and subtypes that were not previously believed to have characteristics of homologous recombination deficiency (clear cell and endometrioid carcinoma, in addition to carcinosarcoma). As mentioned previously, the commonly implicated inherited genes are *BRCA1*, *BRCA2*, *BRIP1*, genes that are part of the Fanconi anaemia pathway (*RAD51C*, *RAD51D*, *BRIP1*, *PALB2* and *BARD1*) and genes involved in DNA mismatch repair (*MSH2*, *MLH1*, *PMS2* and *MSH6*).

Despite genomic data showing recurrent mutations in patients with ovarian cancer, some tumours, particularly the HGSC subtype, are genetically heterogeneous (63, 66, 76), reflecting the underlying genomic complexity of this disease. For example, one study demonstrated intratumor genomic heterogeneity in patients with newly diagnosed HGSC (76).

[H3] HGSC. HGSC has been extensively characterized both at initial diagnosis of ovarian cancer as well as at disease recurrence after exposure to platinum-based chemotherapy (63, 66).

TP53 is the most commonly mutated gene in HGSC (63, 66). *TP53* mutations can be in-frame and frameshift insertions and deletions, as well as missense or nonsense mutations (69). *TP53* mutations frequently occur in the region of the gene encoding the DNA binding domain, but can also occur in regions encoding the non-DNA binding domains. Tumours lacking *TP53* mutations have signs of p53 dysfunction through a copy number gain of *MDM2* or *MDM4*, the gene products of which are involved in the regulation and degradation of p53 (69).

Genomic analyses have revealed defects in homologous recombination in approximately 50% of analysed HGSCs (70, 71). Defective homologous recombination is associated with both germline and somatic *BRCA* mutations, as well as alterations in other DNA repair pathway genes (Figure 3) (63). *BRCA1* is critical for DNA repair, cell-cycle checkpoint control, mitosis, remodeling of

chromatin, and transcriptional regulation; *BRCA2* is important in homologous recombination and DNA repair (72). Hypermethylation of the *BRCA1* promoter has also been shown in a substantial subset of HGSCs but does not influence overall survival and outcome (63).

Additional recurrent molecular alterations identified in HGSC include defective Notch, phosphoinositide 3-kinase (PI3K), RAS/MEK and FOXM1 pathway signalling, as well as a high level of somatic copy number alterations in the genes encoding proteins in these pathways (63). Other mutated genes that play a part in the pathogenesis of HGSC and that could also serve as potential therapeutic targets for ovarian cancer include *AURKA*, *ERBB3*, *CDK2*, *MTOR*, *BRD4*, and *MYC* (63, 77, 78). For example, one study showed that activity of the epigenetic transcription modulator, bromodomain-containing protein 4 (encoded by *BRD4*) is required for the proliferation and survival of HGSC cell lines (77). Also, ovarian cancer cells sensitive to BRD4 inhibition have high expression of *MYC*, another important gene found altered in HGSC (77).

HGSC has been further subdivided using data from gene expression profiling (79, 80). TCGA identified 4 subtypes of HGSC based on gene expression: differentiated, immunoreactive, mesenchymal and proliferative subtypes, which have differences in clinical outcome, although this has not been clinically useful for patient management (79-81). Attempts to more narrowly define the subgroups of HGSC have included integrated genomic analyses incorporating multiple platforms. For example, a micro RNA (miRNA)-regulated network was identified that is associated with the mesenchymal subtype of HGSC and with poor clinical outcomes (82). Some studies have used gene expression profiling to predict the prognosis of patients with advanced-stage HGSC, in addition to treatment resistance and response to platinum-based chemotherapy and PARP inhibitors. However, these studies relied on retrospective analyses and prospective data from randomized trials are still needed to show usefulness of expression assays in subtyping

patients (83).

The level of molecular diversity of HGSC at the time of diagnosis, its evolution, change over time, the presence of few druggable driver mutations and the high rate of copy number alterations in genes of multiple signalling pathways characterizes the genomic complexity of this cancer. Indeed, this molecular complexity provides insight into perhaps why the development of effective therapies for HGSC has been difficult to achieve (63, 66).

[H3] Other epithelial subtypes. The genomic landscapes of other histological subtypes of ovarian cancer have also been studied. Clear cell carcinomas are complex at the genomic level and can have mutations in *ARID1A*, *PIK3CA* and *PTEN* (94). *BRAF* and *KRAS* mutations are common in LGSC (95, 96). Also, LGSC mostly exhibits mutational stability such that the extent of tumour genetic evolution is low in this cancer type in each patient, but these tumours are typically more unresponsive to chemotherapy compared to HGSC (97).

Endometrioid adenocarcinomas frequently carry mutations in *PTEN*, *PIK3CA*, and *CTNNB1* (98). Ovarian cancers associated with endometriosis, such as clear cell and endometrioid carcinomas, are associated with *ARID1A* mutations (98, 99). Low grade endometrioid carcinomas can carry loss of *PTEN* and mutations in *PIK3CA* and *KRAS* (98, 100).

Mucinous carcinomas can carry *KRAS* mutations (102). C>T transitions in an NpCpG trinucleotide context have been shown to be the predominant mutational signature of mucinous carcinomas, indicating deamination of methylcytosines (103). Approximately half of mucinous carcinomas have mutations in *TP53*, with other frequent mutations occurring in *KRAS*, *BRAF*, *CDKN2A*, *RNF43*, *ELF3*, *GNAS*, *ERBB3* and *KLF5* (103).

Hypercalcaemia-associated small cell carcinomas are associated somatic or germline mutations in *SMARCA4* (1, 104).

[H2] Precursor lesions

The distal fallopian tube has been identified as a precursor site of HGSC in a substantial proportion of patients due to the presence of atypical tubal epithelial cells in women with *BRCA1* or *BRCA2* mutations. This site was identified with the discovery of serous tubal intraepithelial carcinoma (STIC) — an early lesion — during risk-reducing bilateral salpingo-oophorectomy in these women, with the presence of STICs in the fallopian tubes of women with advanced-stage ovarian cancer and with identification of precursors in the fallopian tube characterized by DNA damage and mutations in *TP53* (3, 59-61, 87, 88, 91). STIC can be identified in 18–60% of cases of advanced-stage HGSC (3, 59, 60, 86-88) and up to 80% of early stage HGSC. However, STICs are not found in all patients with HGSC and alternative pathways for the pathogenesis of HGSC likely exist (89). One study proposed a dualistic model for HGSC pathogenesis that incorporates the variables of the patient (for example, presence of STIC, *BRCA* status, patient age and morphological features of the HGSC) (91). The study suggested two pathways of HGSC development based on differences in STIC frequency, tumour morphology and outcome, known as classic or SET (>50% solid, pseudoendometrioid, or transitional) pathways. The classic pathway involves the presence of a STIC precursor and a longer timeframe from STIC to development of HGSC. Conversely, the SET pathway typically occurs in younger women, who have a lower STIC frequency and higher level of responsiveness to chemotherapy and PARP inhibitors. The two pathways of HGSC development might have implications for the potential ineffectiveness of risk reducing bilateral salpingo-oophorectomy for some high-risk patients.

[H2] Immune system and tumour microenvironment

Another developing field of research in ovarian cancer pathogenesis is the role of the immune system and the tumor microenvironment. Cytotoxic T -cell infiltration in ovarian cancer has been shown to correlate with improvement in overall survival in several studies (106, 107). For example, antitumor immune responses composed of tumor-reactive T cells and tumour-specific antibodies that can be detected in peripheral blood, ovarian cancer tissue and ascites (108-111). Furthermore, cytotoxic T cell infiltration in ovarian tumours correlates with improvement in overall survival as shown by several groups (106, 107).

Within the many components of the tumor microenvironment, angiogenesis has a critical role in the pathogenesis of epithelial ovarian cancer, promoting tumour growth and metastasis (112). Vascular endothelial growth factor (VEGF) is one of the most potent proangiogenic factors identified in ovarian cancer, with other proangiogenic factors including fibroblast growth factor, angiopoietins, endothelins, IL-8, IL-6, macrophage chemotactic proteins and platelet-derived growth factors also identified (113, 114).

[H2] Chemotherapy-resistance

HGSC and other high-grade ovarian cancer histologies, for example high-grade endometrioid carcinoma, can be further analysed on the basis of platinum sensitivity. Platinum-sensitive ovarian cancers are defined as having a platinum-free interval (PFI; time elapsed between the last dose of platinum-based chemotherapy and evidence of cancer progression) of 6 months or greater, whereas platinum resistant cancers have a PFI of <6 months. In patients with HGSC, one study showed that inactivation of genes by disruption of transcriptional units (gene breakage) can inactivate the tumor suppressors *RBI*, *NF1*, *RAD51B* and *PTEN*, which likely contributes to increasing chemotherapy and platinum resistance (66). Upregulation of the ABCB1 gene encoding for the drug efflux pump multidrug resistance protein 1 (MDR1) leading to MDR1

overexpression could also explain mechanisms of platinum resistance. Also, germline or somatic mutations in *BRCA1* or *BRCA2* could lead to a favorable treatment response with improved responsiveness to chemotherapy (18, 63). Amplification of the 19q12 locus which involves *CCNE1*, (encoding G1/S-specific cyclin-E1, also known as cyclin-E1, which is a cell cycle regulator) was associated with primary platinum-resistant and refractory ovarian cancers (66); this leads to abundance of cyclin E1, which subsequently activates transcription of *BRCA1* and *BRCA2*, elevating levels of the BRCA proteins and leading to platinum-resistance (63).

[H1]Diagnosis, screening and prevention

[H2] Diagnosis

[H3] Clinical presentation. Most women with ovarian cancer are diagnosed in later life, with a median age of diagnosis of 63 years (16). Most women are symptomatic at disease presentation and have ascites (fluid in the peritoneal cavity) and gastrointestinal dysfunction (for example constipation and/or bowel obstruction). Other symptoms at initial presentation include abdominal bloating, abdominal and/or pelvic pain, fatigue, gastrointestinal dysfunction (such as nausea and vomiting, constipation, diarrhoea and gastrointestinal reflux) and shortness of breath (5). Respiratory symptoms can result from extensive intra-abdominal cancer with ascites, causing diaphragmatic pressure, pleural effusions and/or a pulmonary embolus.

Symptoms of ovarian cancer might be initially missed or attributed to other disease processes because they are general and non-specific. Accordingly, diagnosis frequently occurs when the cancer has reached a late stage (either stage III or IV), because symptoms have become apparent and require intervention (5), and/or the symptoms are more-severe, indicative of extensive peritoneal carcinomatosis (cancer of the peritoneum), ascites, and the possible bowel involvement of cancer. The combination of abdominal bloating, increased abdominal size and urinary symptoms has been found in 43% of patients with an eventual diagnosis of ovarian cancer but

only in 8% of patients not diagnosed with ovarian cancer (115). Women presenting with severe or frequent symptoms and those of recent onset warrant further diagnostic investigation because of the association of these symptoms with ovarian masses (155).

Importantly, these symptoms — and their late presentation — largely apply to those with HGSC. By contrast, histologies such as clear cell and small cell carcinoma can become symptomatic at an earlier stage. For example, hypercalcaemia can be the initial presentation of clear cell or small cell carcinomas. These tumour types are also associated with many of the same symptoms observed with more advanced HGSC, such as abdominal distension, pelvic pressure and/or pain, as well as pressure of the ovarian mass on the bowel or urinary tract system. Most patients with clear cell carcinomas present at an early stage and might present with symptoms related to pelvic pressure.

[H3] Diagnostic work up. In patients with indicative symptoms diagnostic work up includes physical examination of the patient, consisting of pelvic examination and recto-vaginal examination, in addition to radiographic imaging (transvaginal ultrasonography, abdominal ultrasonography, CT, MRI and/or PET (Figure 2)). The CA125 blood test can also be used in combination with other diagnostic tests for the detection of ovarian cancer. Laparoscopic surgery with removal of the mass is recommended (116) and will also give further information on the tumor histology. Results from diagnostic testing, especially transvaginal ultrasonography, can give information regarding the ovarian mass such as size, location and level of mass complexity, which can help clinicians determine the level of suspicion for cancer (ref). More advanced cancer is associated with ascites and peritoneal carcinomatosis within the abdominal cavity; in order to confirm a diagnosis of ovarian cancer, a tissue biopsy must be performed.

[H3] Staging. Pathological evaluation and tumour staging of ovarian cancer is based on surgical assessment of the cancer at initial diagnosis, including removal of lymph nodes, tissue biopsy and abdominal fluid and uses the International Federation of Gynecology and Obstetrics (FIGO) staging system (Table 3). The staging system has recently changed with acceptance of the common, Müllerian-derived multicentric origin of ovarian, fallopian tube and peritoneal cancers and that these cancers should be grouped using one system (127). The latest FIGO staging system has three other notable characteristics: stage IC tumours have been subdivided based on the mechanism underlying rupture of the ovarian capsule and the presence of malignant ascites (the presence of tumour cells in ascites), stage IIC has been eliminated and stage III has a clearer definition that encompasses the size of metastases as well as the presence of metastases to the lymph nodes. Moreover, stage III was reclassified to account for differences in the clinical outcomes in patients with metastases to the lymph nodes who do not have peritoneal carcinomatosis, versus patients with peritoneal carcinomatosis (128, 129). Additionally, stage IV has been further divided into stage IVA, and IVB. The FIGO staging system recommends that the primary tumour site (the ovary, fallopian tube or peritoneum) and the histological grade be stated in either the operative report and/or the final pathology report (127).

Surgical staging of ovarian cancer by gynaecological oncologists has been shown to be superior to that performed by non-oncological (general) surgeons as have patient outcomes (138–140). Indeed the issue with accurate staging is pertinent; one study found that only 54% of women with ovarian cancer received correct staging as determined by a gynecologic oncologist (141). When patients are operated by non-gynecologic oncologists, such as general surgeons or general gynecologists, the diaphragm was not visualized in 86% of cases and the omentum was not biopsied in 68% of cases (141), meaning cancer was commonly missed in the diaphragm, pelvic peritoneum, peritoneal fluid and omentum.

[H2]Screening

No current screening strategy has affected survival of patients with ovarian cancer. Creation of a successful screening strategy for ovarian cancer is challenging because this is not a common disease and includes a range of histological subtypes, each with different biological and clinical properties. For example, patients with LGSC have substantially better overall prognoses than patients with more-aggressive, high grade cancers and might require a different screening strategy (95).

The CA125 blood test is not an effective screening test when used alone, given that CA125 is only elevated in 50% of stage I ovarian cancers and can also be increased in benign disorders such as uterine fibroids, ovarian cysts and other conditions such as liver disease and infections (117, 118). CA125 elevation is most frequently observed in HGSC, with lower levels of CA125 in other non-serous subtypes (ref).

Combining the CA125 blood test and radiographic imaging, such as transvaginal ultrasonography, has been evaluated for use as a screening strategy. One of the largest studies to examine this combination was the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial (120), which enrolled 78,216 women between the ages of 55–74 years. Women were randomly assigned into two groups of approximately equal size, to receive either annual screening (encompassing yearly CA125 tests for 6 years and transvaginal ultrasonography for 4 years) or usual care (no yearly CA125 or transvaginal ultrasound, but could have undergone bimanual examination with ovarian palpation). Ovarian cancer was diagnosed in 212 women (5.7 per 10,000 person-years) in the screening group and in 176 women (4.7 per 10,000 person-years) in the usual care group (rate ratio 1.21; 95% CI=0.99–1.48) (5) and the stage distributions of cancer were similar for the two groups (stage III and IV cancers comprised almost 80% of cancers in both groups). Also, no significant reduction in overall mortality was

observed with screening (3.1 deaths per 10,000 women in the screened group and 2.6 deaths per 10,000 person-years in the usual care group; mortality rate ratio of 1.18 (95% CI= 0.82–1.71)) (5)

Although the CA125 tested alone as a screening marker has been deemed ineffective, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) study evaluated the strategy of longitudinal measurements of CA125 levels has also been assessed for screening of ovarian cancer, in an algorithm termed ‘risk of ovarian cancer algorithm’ (ROCA) (5, 7,123). In one arm of this study, ROCA was the primary screening modality with transvaginal ultrasonography used as a secondary screening measure based on CA125 levels (7). The ROCA algorithm interpreted longitudinal CA125 data and triaged women to either normal (annual screening), intermediate (repeat CA125 testing in 3 months) and elevated risk (repeat CA125 testing and transvaginal ultrasonography in 6 weeks). Annual screening used transvaginal ultrasonography as the primary test, following which, patients were subdivided into 3 groups based on ultrasonography results; normal (annual screening), unsatisfactory (repeat in 3 months) and abnormal (scan with a senior ultrasonographer within 6 weeks). In this study, 202,638 women were randomly assigned into one of three groups (screening based on the ROCA algorithm, ultrasonography alone and no screening) (7) and followed-up for a median period of 11.1 years. The proportion of women diagnosed with ovarian cancer was similar between groups (between 0.6–0.7%), but lower stages (stage I-IIIa) of disease was in a higher proportion of patients in the ROCA screened group than in those who were not screened ($P < 0.0001$). However, there was no difference between patients in the ROCA group and those who received transvaginal ultrasonography ($P = 0.57$). Mortality reduction was not significant between any of groups, therefore, the ROCA test cannot currently be recommended as a screening strategy for ovarian cancer; further follow-up of this study is necessary to understand the long-term potential of this screening strategy.

WAP four-disulfide core domain protein 2 (also known as human epididymis protein 4 (HE4))

has also been tested as a potential biomarker for use in ovarian cancer screening (124). A systematic review reported better sensitivity, specificity and likelihood ratios for HE4 compared with CA125, but this has not yet been analysed within a screening strategy (125). The use of other novel markers for ovarian cancer screening are under investigation, including, for example, DNA analysis of uterine lavages or Pap smears for *TP53* mutations (126).

[H2] Prevention

Salpingectomy has gained favour as a prevention technique based on the presence of precursor lesions in the fallopian tubes of some women with ovarian cancer as discussed above. However, no randomized prospective studies have been performed to determine the benefit or evidence of risk reduction following salpingectomy (39-41).

The Society of Gynecologic Oncology guidelines and recommendations for the prevention of ovarian cancer. These guidelines, in addition to others, recommend all women with invasive ovarian cancer (regardless of family history, histology or age) should undergo genetic testing and genetic counseling. The purpose of this testing is to assess women for the presence of a high risk gene which could convey increased risk for both the individual and family members, as well as having implications for outcome and therapeutic management (57, 58). Moreover, the Society of Gynecologic Oncology guidelines recommend performing risk-reducing bilateral salpingo-oophorectomy in women aged 35–40 years who are at increased genetic risk (the presence of germline mutations in high risk genes) of developing ovarian cancer, as well as individualizing the age at which women undergo risk-reducing surgery (57). Also, the Society of Gynecologic Oncology guidelines mandate and recommend microscopic examination of the entire ovary and fallopian tube following risk-reducing bilateral salpingo-oophorectomy in high-risk women, to rule out early invasive cancers (57, 59-61).

The annual risk of ovarian cancer in individuals of specific age groups with germline *BRCA* mutations and intact ovaries has been estimated, to help guide clinicians and patients about appropriate timing of the risk-reducing bilateral salpingo-oophorectomy (62). In one study, risk-reducing salpingo-oophorectomy reduced risk of ovarian cancer in women with *BRCA* mutations by 80%. Timing of risk-reducing bilateral salpingo-oophorectomy is important, as performing surgery in women < 45 years of age has been associated with an increased risk of cardiovascular disease, osteoporosis and osteopenia (57); oestrogen replacement should be considered in these patients (if they have not had breast cancer), but the benefits and potential risks or optimal duration of oestrogen therapy has not been determined (57).

Variants of unknown importance occur in *BRCA1* and *BRCA2*, as well as other high risk genes implicated in ovarian cancer, but the effects of these variants on ovarian tumorigenesis are currently unknown (75). Variants of unknown importance represent dilemmas for women who are diagnosed with them, as these variants carry an unknown cancer risk, meaning patients and their family members cannot be accurately counseled about risk reduction and preventative surgeries.

[H1]Management

At initial diagnosis, patients are faced with the challenge of accessing appropriate medical treatment and quickly making complex decisions about their care. The choice of physician can impact outcomes (130, 131) as can adherence to the guidelines for the standard of care (132, 133); surgery performed by a gynecologic oncologist results in superior outcomes and survival, compared with surgery performed by a non-gynecologic oncologist, such as a general surgeon.

The primary aim of treatment for ovarian cancer is to maximize cancer control and to palliate disease symptoms for as long as possible. Surgery performed by a gynecologic oncologist is the main treatment for most patients with ovarian cancer. The extent of surgery is determined by the

stage of cancer and patient factors; for example, women with more advanced cancer might undergo bilateral oophorectomy, but women with low risk, stage I cancer (such as mucinous histologies) and young women who wish to preserve fertility, might undergo unilateral oophorectomy of the affected ovary only. Surgical cytoreduction results are frequently referred to as suboptimal (meaning any focus is ≥ 1 cm in size, R2 resection), optimal (meaning < 1 cm residual cancer, R1 resection) or no evidence of residual macroscopic disease (R0 resection). New studies only define optimal surgical results if macroscopic complete resection of the cancer has been achieved. Patients with macroscopic complete resection (R0) following surgery have significant improvements in outcomes, such as overall survival and progression-free survival (PFS), compared with patients with remaining post-operative visible disease (135, 136). For example, in one study (GOG 182) patients with stage III or IV ovarian cancer with optimal cytoreduction had a worse prognosis than patients with no evidence of residual macroscopic disease or R0 followed by platinum-based chemotherapy. Nevertheless, patients with optimal cytoreduction have a significantly better median PFS and overall survival than patients with suboptimal cytoreduction (134-136).

[H2] Newly diagnosed ovarian cancer

[H3] Primary surgery. The primary treatment for women with newly diagnosed ovarian cancer is primary surgical cytoreduction (Figure 4). The primary goal of surgery is to achieve macroscopic complete resection of disseminated carcinomatosis, often involving complex surgical techniques, including *en bloc* resection of the bowel, uterus and adnexal masses, as well as peritonectomy. In some cases, colonoscopy and/or upper endoscopy might be required, to rule out the possibility of a primary gastrointestinal cancer, rather than a primary ovarian cancer. Systematic pelvic and paraaortic lymph node dissection is also necessary in patients with high-risk early stage ovarian cancer, or patients with stage II and IIIA disease, because nodal metastases signify a higher stage of disease, poorer prognosis and the need for different treatment

strategies.

It is critical for the surgeon to define the best surgical approach and determine the appropriateness of surgery prior to administration of chemotherapy versus NACT. If NACT is to be administered, a biopsy is needed to confirm pathology consistent with an ovarian, tubal or peritoneal primary cancer, before chemotherapy can be commenced.

[H3] Adjuvant chemotherapy. Recommendations for the use of adjuvant chemotherapy using platinum-based chemotherapy for patients with early stage ovarian cancer depend on cancer stage, grade and histology. Many patients with grade I, stage I cancer are not treated with chemotherapy post-surgery but those with higher grades (\geq grade II) and/or specific histologies (such as HGSC and clear cell carcinomas) undergo adjuvant systemic platinum-based chemotherapy (142). Indeed, several first-line adjuvant systemic chemotherapy strategies have led to an improvement in overall survival for patients with newly diagnosed, advanced-stage ovarian cancer including the addition of paclitaxel to platinum-based chemotherapy agents, use of intraperitoneal cisplatin in patients with optimally cytoreduced cancer and incorporation of dose-dense weekly paclitaxel treatment instead of administration every 3 weeks (7, 143-145).

Studies have examined the efficacy of different combinatorial treatments to optimize adjuvant chemotherapy, including combinations of platinum-based chemotherapy agents (cisplatin and carboplatin), taxanes (paclitaxel, docetaxel), anti-angiogenic agents (bevacizumab, nintedanib, trebananib and pazopanib) and other drugs (pegylated liposomal doxorubicin, gemcitabine) (Table 4).

In 2011, the European Medicines Agency (EMA) approved the use of bevacizumab as an addition to carboplatin/paclitaxel chemotherapy and maintenance therapy in patients with newly diagnosed, advanced-stage ovarian cancer, based on the improvement in PFS in the GOG218 and ICON7 studies (Table 4). A retrospective analysis of the ICON7 study of patients with

suboptimally cytoreduced stage IIIC or stage IV cancer showed an overall survival benefit with the addition of bevacizumab to a carboplatin/paclitaxel backbone, but no improvement in overall survival was observed in the intent to treat population of patients entered in either ICON7 or GOG 218 (151-153). Despite being available in Europe, bevacizumab has not been approved for patients in the United States, making collaborative trial design for both newly diagnosed and recurrent ovarian cancer challenging.

[H3] Neoadjuvant chemotherapy. NACT consisting of carboplatin and paclitaxel for 3 cycles is then followed by interval (meaning between rounds of chemotherapy) surgical cytoreduction and additional chemotherapy post-surgery for a total of 6 cycles of chemotherapy. NACT is a possible treatment alternative to upfront surgical cytoreduction for ovarian cancer, especially for patients who are too ill for initial surgery or if the cancer burden is too extensive to allow macroscopic complete resection. Two trials have demonstrated comparable outcomes for first-line surgery with adjuvant chemotherapy, compared with NACT followed by surgery and post-operative chemotherapy, with less morbidity and mortality but similar outcomes in PFS and overall survival in the group that received NACT (160, 161). Data from the first study showed NACT followed by interval cytoreductive surgery is not inferior to primary cytoreductive surgery followed by chemotherapy and no significant difference in PFS (12 months) or overall survival (29–30 months) was found between groups (160). The second study (CHORUS) in patients with advanced stage III or IV cancer randomly assigned to either primary cytoreductive surgery followed by chemotherapy (consisting of either carboplatin and paclitaxel or carboplatin alone), or to NACT (3 cycles), followed by cytoreductive surgery and three more cycles of chemotherapy (carboplatin and paclitaxel or carboplatin alone) showed a non-significant difference in overall survival between the group that received NACT (24.1 months) and those that received upfront surgery (22.6 months; 95% HR 0.87, 95% CI 0.72–1.05) (161). Additionally, PFS was similar for both groups; 12.0 months in the NACT group, compared with 10.7 months for the primary

surgery group (HR 0.91, 95%CI: 0.76–1.09). However, the number of post-operative deaths was lower in the NACT group compared to the upfront surgery group (161).

Some medical centres are testing the use of surgical algorithms with diagnostic laparoscopy to determine tumour resectability, to identify patients who are appropriate for first-line cytoreductive surgery, versus those suitable for NACT, but no validated preoperative instrument has currently been established (162). Controversy persists over the identification of the most appropriate candidates for NACT and whether NACT induces upfront platinum resistance. Accordingly, a general consensus regarding the equivalence of NACT followed by surgery and upfront surgery followed by adjuvant chemotherapy is lacking (163). Also, some groups have argued that the overall survival and PFS outcomes used in the aforementioned randomized trials of NACT versus upfront surgical cytoreduction (160, 161) are inferior to other trials and that inferior complete resection rates were observed in the primary surgery control group, particularly in the CHORUS study (164, 161).

[H3] Maintenance therapy following NACT. Aims of maintenance therapy are to prolong a clinically meaningful survival endpoint, such as PFS and also preserve a patient's quality of life. The use of maintenance therapy following platinum-based chemotherapy has been investigated and reviewed (165, 166). Monthly paclitaxel treatment (for a duration of either 3 months or 12 months) has been assessed in patients with ovarian cancer following completion of NACT (167); no benefit in overall survival was observed with 12 month paclitaxel treatment, compared to treatment for 3 months, but PFS was longer in the 12-month versus 3-month groups. However, due to the risk of developing adverse effects with continuation of monthly paclitaxel for 12 months (for example, alopecia and peripheral neuropathy), the use of paclitaxel for maintenance

therapy after platinum-based chemotherapy is not commonly used; currently, the standard of care following completion of platinum-based chemotherapy is observation alone (142).

Pazopanib has also been studied for use in maintenance therapy, resulting in an increase in PFS, but no improvement in overall survival (156). Pazopanib is also associated with a significant toxicity profile such as fatigue, gastrointestinal toxicities (such as nausea and/or diarrhoea), hypertension and myelosuppression (156).

Bevacizumab is approved in Europe as maintenance therapy following initial platinum/taxane/bevacizumab chemotherapy based on GOG218 and ICON7 results.

[H2]Recurrent disease

[H3] Monitoring for recurrence

>80% patients with advanced-stage ovarian cancer will experience recurrence of their primary cancer. Recurrent ovarian cancer is generally incurable, but rare exceptions to this exist, such as patients with isolated metastatic cancer in whom the disease can be fully resected after secondary cytoreductive surgery or treatment with localized radiotherapy.

Many patients with recurrent ovarian cancer are asymptomatic at the time of their relapse and as such, recurrent ovarian cancer is most frequently detected by elevation of CA125 levels; the sensitivity and specificity of this test for recurrence detection range from approximately 60–94% and 91–100%, respectively (168, 169). CA125 levels are monitored following completion of initial treatment, but guidelines regarding the frequency of CA125 and clinical monitoring of patients with ovarian cancer changes with differing guidelines (168, 169). The Society of Gynecologic Oncology recommends a review of clinical symptoms and a physical examination of patients following initial treatment for ovarian cancer every 3 months with an optional CA125 test and radiographic imaging (CT, PET or MRI) in patients with suspected recurrence (such as those with an elevated CA125, findings upon clinical examination and/or suspicious symptoms)

(169). Conversely, the National Comprehensive Cancer Network guidelines recommend follow-up visits every 2–4 months for 2 years after treatment, including assessment of CA125 levels and radiographic imaging if recurrence of ovarian cancer is indicated (142).

The limitations of disease detection and the role of CA125 should be discussed with all patients who have completed therapy. Sufficient clinical information should be available to make a definitive diagnosis of cancer recurrence, including elevated CA125 levels, radiographic evidence of cancer, physical exam evidence, symptoms related to the disease burden and/or a positive biopsy. Elevated CA125 in the absence of other clinical indicators is generally not a reason to initiate treatment, unless the patient is enrolling into a clinical trial. Some patients might not have elevated CA125 levels at either initial diagnosis or with recurrence of ovarian cancer, which makes the CA125 test less useful when used for recurrent cancer. In these patients, alternative biomarkers, such as HE4 and/or the use of interval radiographic imaging might be of use for monitoring of recurrent cancer, but this needs further evaluation. Although used, CA125 for the early detection of recurrence has not been shown to improve outcomes in patients with recurrent disease. In one study, no improvement in patient survival was observed following early treatment of recurrent ovarian cancer (diagnosed on the basis of increased CA125 levels in the absence of clinical symptoms), compared with delayed treatment (until the manifestation of clinical symptoms of disease progression) (170). This trial has been criticized because of the long period of time needed to accrue patients (almost 10 years), the lack of predefined subsequent therapies and the lack of access to newer treatments (such as bevacizumab) and other drugs through clinical trials, or to the potential use of secondary cytoreductive surgery (ref).

[H2]Treatment options

Following definitive diagnosis of recurrent ovarian cancer, several factors should be considered before deciding appropriate treatment options, including the level of disease burden (such as, symptomatic versus asymptomatic cancer and the location of metastases), the presence of

complications from previous therapies (such as peripheral neuropathy, pancytopenias and/or drug hypersensitivity reactions), availability of clinical trials, degree of platinum sensitivity, end organ function, performance status of the patient and also, wishes and goals of the patient. Treatment of recurrent ovarian cancer has been made more complex, with oncologists factoring in tumour histology and underlying *BRCA* status, given the recent FDA and EMA approvals of the PARP inhibitor olaparib.

Secondary surgical cytoreduction can be considered for patients with a long platinum free interval with recurrent cancer that is limited and isolated, such as cancer in one location such as the spleen or an isolated lymph node, although meta analyses did not demonstrate any benefit of this surgery (172). One randomized trial (GOG 213) investigating the efficacy of secondary surgical cytoreduction for the treatment of platinum-sensitive recurrent ovarian cancer is underway (171). The German AGO Study Group (Arbeitsgemeinschaft für Gynäkologische Onkologie) has demonstrated a potential survival benefit only in patients with no postoperative residual cancer following secondary cytoreductive surgery (173). This study also established a preoperative clinical score to predict the target population with the best outcomes following secondary cytoreductive surgery including the amount of ascites (<500ml) and result of primary surgery (macroscopically free). On the basis of these findings, a prospective study was conducted comparing the overall survival of patients with platinum-sensitive recurrent ovarian cancer undergoing cytoreductive surgery followed by platinum-based chemotherapy, with patients receiving chemotherapy alone (DESKTOP-Trial III), results of which are expected in 2017 (174).

Recurrent ovarian cancer is classified as platinum-sensitive or platinum-resistant as defined above. However, the Institute of Medicine called for an improved classification system for recurrent ovarian cancer, as the current classification does not reflect the effect of *BRCA* status on treatment responses and the varied responses to treatment in women with platinum-resistant

cancer (179). Additionally, some groups have called for diminishing the importance of the PFI as this definition is flawed, with no universally accepted objective definition and instead, incorporating key disease parameters such as molecular signature (such as *BRCA* mutation), immunological features and tumor histology (178).

[H3] Platinum-sensitive disease. For patients with platinum-sensitive recurrent ovarian cancer, the standard of care is re-use of a platinum-based regimen (142). However, re-use of platinum-based chemotherapy is associated with the development of potentially life threatening platinum drug allergies (177). Response rates in patients with platinum-sensitive recurrent cancer are approximately 50% (142, 180-182), although the length of the PFI decreases with subsequent platinum use (ref). Various combinations of therapies are being investigated for the treatment of platinum-sensitive ovarian cancer (Table 5), including paclitaxel/carboplatin (180), carboplatin/pegylated liposomal doxorubicin (181) and carboplatin/gemcitabine (182). Use of a platinum based combination has been shown to improve outcomes compared with the use of single agent platinum in patients with a platinum sensitive recurrence (ref)

Approved therapies for the treatment of patients with recurrent, platinum sensitive ovarian cancer in Europe include bevacizumab (in combination with carboplatin and gemcitabine) and trabectedin (an agent that binds to DNA, resulting in cell cycle arrest and apoptosis) (182). Carboplatin and gemcitabine are approved for use in the United States. Trabectedin was not ultimately approved for use in the United States due to toxicity concerns; adverse effects of this agent include bone marrow suppression, fatigue and gastrointestinal complications (such as nausea, vomiting and diarrhoea), in addition to elevation of liver enzymes.

Olaparib has been approved by the EMA as a maintenance therapy for platinum-sensitive ovarian cancer, after response and completion of platinum-based chemotherapy in patients with either a

germline or tumour *BRCA* mutation. However, accelerated approval for olaparib as a maintenance therapy in patients with germline *BRCA* mutations was rejected by the FDA's Oncologic Drugs Advisory Committee, due to a lack of evidence supporting improvements in overall survival; the final results of a confirmatory phase III study (SOLO2) will likely factor into future FDA decisions (203, 204). Nonetheless, the FDA granted accelerated approval to olaparib as a single agent for use in patients with germline *BRCA* mutations who have received at least three prior lines of chemotherapy, regardless of platinum sensitivity (205).

[H3] Platinum-resistant disease. For patients with platinum-resistant cancer, bevacizumab with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan treatment in the first platinum-resistant setting was approved by both the FDA and EMA, following the results of the AURELIA trial (187, 188). Although promising, care should be taken when using bevacizumab in patients with ovarian cancer, due the risk of severe adverse effects, such as gastrointestinal perforation (189), hypertension, proteinuria and fistula development. Other single agents available to treat platinum-resistant ovarian cancer include gemcitabine, etoposide and navelbine (142), which have response rates of up to 10-15% and median PFS of approximately 3-4 months.

Anti-angiogenic agents that have been studied in recurrent ovarian cancer include nintedanib, trebananib, sunitinib, cabozantinib, and cediranib (190, 191). Notably, cediranib has single agent activity in both platinum-resistant and platinum-sensitive recurrent ovarian cancer (192), can increase PFS when combined with platinum-based chemotherapy and can also be used as maintenance therapy in patients with platinum-sensitive recurrent cancer (185). Also, cediranib is being tested in combination with olaparib in two actively accruing phase III studies, GY004 and GY005 (193 and 194).

Ultimately, treatment of recurrent ovarian cancer should be tailored to the patient to prevent worsening of pre-existing adverse effects such as myelosuppression and neuropathy, as well as

respecting the patient's wishes and the avoidance of other adverse effects such as alopecia and gastrointestinal complications.

[H1]Quality of life

The diagnosis of any life threatening disease, coupled with the acute and long-term adverse effects of treatment, can be associated with reductions in quality of life domains, including physical, functional, emotional, sexual, social and occupational well-being. Moreover, the large number of medical decisions required in a short period of several days to weeks following initial diagnosis of ovarian cancer can add to the emotional stress felt by patients. The responses to these issues varies; for example, some patients might re-evaluate their attitudes to relationships, work and day-to-day life following a diagnosis of ovarian cancer (220).

Although current treatment advances give more women with ovarian cancer the prospect of living longer, minimizing and/or ameliorating the adverse effects associated with treatments is crucial if quality, as well as length, of life is to be improved. Improvements in PFS or overall survival in trials might excite clinical scientists, but be of less value to patients experiencing treatment-related adverse effects; because of this, many phase III studies have incorporated standardized, validated quality of life measures (commonly referred to as patient reported outcome (PRO) end points) into studies (221, 223). PROs are important as there are increasing doubts raised about the validity of data regarding adverse events collected during clinical trials; several studies have shown that the symptoms of disease and adverse effects of treatment are often under-recognized, under-reported and consequently under-treated (224). Indeed, patients report adverse effects (such as fatigue, nausea, vomiting, constipation, alopecia, appetite loss and pain) occur earlier, more frequently and of greater severity than do clinicians and nurses using Common Terminology

Criteria for Adverse Events (CTCAE) grading or proxy raters (224).

Quantification of quality of life issues faced by women with ovarian cancer requires well-constructed, reliable PRO measures that need to be essential components of phase III studies. Both the FDA and EMA have clear guidelines on PRO instruments that are acceptable for conducting health technology assessments, defined as outcomes reported by patients, without the intervention of a third party and that have been constructed using appropriate psychometric methodology (225). One key issue is that the PRO measures should be defined upfront and during trial development, with patients involved in their production. PRO measures used for ovarian cancer include generic, tumor-specific, treatment-specific or symptom-specific measures (226, 228, 229) and involve face-to-face interview schedules (230), quality of life questionnaires (227-229, 231, 232), satisfaction scales and patient preference approaches (233).

For example, a PRO might include a series of questions related to the severity of various symptoms, such as lack of energy, pain, discomfort, sexual dysfunction, feeling ill, insomnia, sweating, bowel control and constipation, as used in the GY004 trial.

Thorough monitoring using validated instruments within clinical trials is needed to compile a database of the trajectory and severity of issues such as adverse effects of treatment, in addition to emotional distress, permitting better evaluation of the benefits and harms of therapies, but also to establish the case for more research to develop therapies to reduce the adverse effects. The traditional end points of clinical trials (such as PFS and overall survival) need to be integrated with PROs in order to improve quality as well as quantity of life.

[H1] Outlook

Now is a very exciting and promising time for ovarian cancer research, yet challenges remain in early detection, identification of women who are at higher risk of developing ovarian cancer, overcoming platinum resistance and resistance to other treatments, in addition to developing rationale and effective immunotherapeutic strategies.

With the fields of genomics yielding more genetic information about ovarian cancer, in addition to the genotype of patients and with costs of sequencing dropping, understanding the pathophysiology and rationale design of therapeutics are poised to move forward. In fact, the National Comprehensive Cancer Network genetics guidelines as well as several European organizations have recommended universal germline *BRCA* mutation screening for all women diagnosed with ovarian cancer, in order to identify family members at high risk and the risk of the patient developing other cancers besides ovarian cancer, to allow performance of risk-reducing surgeries. Moreover, the extent of genetic testing, including panel testing that includes genes other than *BRCA1* and *BRCA2*, continues to evolve and will contribute to our understanding of the genetics underlying formation of ovarian cancer and its biology. Improved understanding of the genomics of different histological subtypes of ovarian cancer will be an important target over the upcoming years, to facilitate the understanding of the risk factors associated with this disease, as well as development of prevention and therapeutic strategies.

Early detection efforts are promising, with ROCA testing demonstrating increased detection of early ovarian cancers, compared with no testing. However, results of the UKCTOCS study did not show an overall survival advantage to using the ROCA thus no screening test exists at this time. Additionally, further research elucidating the role of variant of unknown importance in both *BRCA* genes and in other associated genes (such as *BRIP1* and *RAD51*) in the risk of developing ovarian cancer is critical for the appropriate recommendation of risk-reducing surgeries.

Other risk-reducing efforts, including surgical techniques such as bilateral salpingectomy, that are

not directed at the high risk population but more at a general risk population are ongoing.

Understanding the pathogenesis of the various types of ovarian cancer, such as the precursor STIC lesions for HGSC, is critical for the appropriate use of surgical interventions for prevention of ovarian cancer. Establishing uniform criteria for the definition of the site of origin of HGSC, based on specific pathology findings, is being called for by consensus statements (93).

[H2] Emerging therapies

Promising future therapies for ovarian cancer include PARP inhibitors and antibody–drug conjugates. PARP inhibitors, initially olaparib, have shown single agent response rates of up to 30% in recurrent ovarian cancer with the greatest activity in cancers with *BRCA* mutations and in platinum-sensitive disease (197-199). Other PARP inhibitors (such as niraparib, rucaparib, and veliparib) that have single agent activity in ovarian cancer, are in phase III studies of, for example, use as maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer, following a response to treatment with platinum-based chemotherapy (206, 207) (Table 6); rucaparib was recently given breakthrough status (to accelerate the development and review of the drug) by the FDA based on results from the ARIEL2 trial (208). Veliparib has been added to the NACT armamentarium with carboplatin and paclitaxel for newly diagnosed advanced ovarian cancer in a phase III study, in addition to testing as a maintenance therapy (209).

Acknowledging that the effectiveness of single agent biologic therapies has reached a therapeutic plateau, one promising approach has been the development of combinations of biological agents (anti-angiogenics, PARP inhibitors, and immunotherapy agents) (236, 237, 241, 242). Such a strategy would target multiple cancer-promoting pathways or mechanisms and might be effective in particular in HGSC due to its genomic complexity. Other histological subtypes such as clear cell carcinoma that can harbor deficiencies in homologous recombination, such as mutations *ARID1A* and *PIK3CA*, might also be clinically responsive. Furthermore, biologic combinations

have the advantage of including agents that have non-overlapping adverse effects that might potentially reduce treatment-related toxicities.

Combining PARP inhibitors with targeted therapies against the PI3K pathway is being investigated, based on pre-clinical evidence from patient-derived xenograft models.

Combinations of PARP inhibitors and, for example, CDK inhibitors, immunotherapy agents and HSP90 inhibitors (239, 240) are also being assessed. Combining PARP inhibitors with chemotherapy has already proved challenging due to overlapping myelosuppression associated with both therapies.

Study of immunotherapy strategies for treatment of recurrent ovarian cancer is underway (213) with several immune checkpoint inhibitors tested in recurrent disease (Table 6). At this time, many questions remain about the optimal strategies for the use of immunotherapies for the treatment of either newly diagnosed or recurrent ovarian cancer, but several studies are planned and are underway. Combinations of either chemotherapy and immunotherapy or two immunotherapy agents are under investigation. For example, nivolumab and ipilimumab (which has shown efficacy in melanoma) compared with nivolumab alone is being investigated, results from which are pending (235). More research is needed to understand the selection of optimal immunotherapy through the use of biomarkers, the effect of the tumor microenvironment on cancer growth and determining best and most effective therapeutic agents and combinations.

Antibody–drug conjugates have shown single agent activity. One antibody drug conjugate, IMGN853, targets the folate- α receptor and is linked to a highly potent maytansinoid that targets microtubules and suppresses microtubule dynamic instability, inducing cell-cycle arrest and cell

death (219). IMGN853 has demonstrated impressive single agent activity in patients with recurrent platinum-resistant ovarian cancer (219).

One other strategy for therapeutic management of ovarian cancer is replacing mutated *TP53* using gene therapy, as well as inhibition of MDM2 the ligase regulating p53 levels through small molecules). However, *TP53* gene therapy using adenoviral vectors has been met with limited success partly due to toxicity related to the approaches used (157, 158). Other emerging therapies targeting tumors carrying mutant *TP53* include COTI-2, which is thought to induce a ‘wild-type-like’ conformational change in mutant p53 and is currently in clinical trials (159).

[H3] Importance of tumour histology. With the improved understanding that ovarian cancer is composed of several histologically and molecularly distinct subtypes, certain classes of therapeutics have histology-specific mechanisms of action, such as PARP inhibitors for treatment of HGSC and MEK inhibitors for treatment of LGSC. Activity of the MEK inhibitor selumetinib in LGSC has been demonstrated (210); clinical trials comparing the use of MEK inhibitors to chemotherapy for the treatment of recurrent LGSC are underway; including a phase III study of binimetinib (also known as MEK162), compared with physician’s choice of chemotherapy agent (MILO study) (211). However, the MILO study was terminated because of futility, based on a planned interim analysis showing that the hazard ratio for progression free survival crossed a predefined futility boundary. One other study assessing MEK inhibition for the management of LGSC is investigating trametinib (GSK 1120212) in patients with recurrent or progressive LGSC (212), but this study has been suspended due to problems with the drug supply.

[H3] Drug approvals. One challenge for the development of new therapies in ovarian cancer is the approval mechanisms of the FDA and EMA. Demonstrating an improvement of overall survival is a requirement for regulatory approval, but is difficult to demonstrate in ovarian cancer; explanations for this are not fully understood, but possibly include the use of active study agents after disease progression, which dilutes the effect of the active agent on overall survival but not on PFS (243, 244). Additionally, the lack of subclassification of histologic subtypes for clinical trial eligibility might have diluted the efficacy of some therapeutic agents, such as bevacizumab and also because no biomarker currently exists to select patients to receive this therapy. Several groups are calling for the achievement of significant improvement in PFS, coupled with PRO measures demonstrating the benefit of treatment, as a reason for drug approval; approval of bevacizumab and olaparib was due to improvement in PFS, quality of life, duration of response or response rate though approvals based on PRO's are rare (ref). The time frame between subsequent therapies (that is, the second PFS) or time between paracentesis or thoracentesis procedures could also be important measurements of patient benefit from a specific therapy. PROs should be a vital component of any phase III study, particularly those testing agents for potential regulatory approval for the treatment of ovarian cancer.

Figure 1. Histological subtypes of ovarian cancer.

a | High grade serous carcinoma (HGSC) is characterized by severe nuclear atypia, high nuclear to cytoplasmic ratio and abundant mitoses. Papillary architecture (arrow) is also often present. b | Serous tubal intraepithelial carcinoma (STIC) lesions share the same morphological features as HGSC, with severe atypia, mitoses and lack of polarity. STIC lesions are thought to be precursors for HGSC. c | Low grade serous carcinoma (LGSC) demonstrates papillary architecture, but only mild nuclear atypia and a lower nuclear to cytoplasmic ratio. d | Clear cell carcinoma is characterized by large atypical tumor cells with frequent clearing of the cytoplasm and stromal hyalinization. e | Endometrioid adenocarcinoma is characterized by gland formation that recapitulates endometrial glands and is graded based on cellular architecture and nuclear atypia. f | Mucinous adenocarcinoma shows mucin-filled tumour cells, with frequent goblet cell forms present.

Figure 2. CT scans from a patient with stage IV ovarian cancer

a | Right and left pleural effusions (arrows). b | Peritoneal carcinomatosis (arrows) . c | Large volume ascites and a peritoneal hepatic implant (arrows)

Figure 3. DNA repair mechanisms and ovarian cancer. A | The double-stranded break and homologous repair process begins with recognition of the damage by serine-protein kinase ATM (ATM); a series of steps leads to the recruitment of the BRCA complex. B | DNA mismatch repair is mediated by the MSH proteins, as well as the endonuclease PMS2 and PCNA. These DNA repair processes are aberrant in ovarian cancer owing to mutations in the proteins involved.

Figure 4. Tumour burden in ovarian cancer.

A | Surgical removal of ovarian tumours in a 63 year old patient with bilateral advanced stage high grade serous ovarian (HGSC) cancer. B | : Bilateral HGSC with peritoneal carcinomatosis and involvement of intestinal surfaces C: removal of a serosal tumor implant located on the surface of the liver

Table 1. Characteristics of ovarian cancer by histology, genomic characteristics, and active therapies

Histological subtype	Clinical findings	Genetic characteristics	Treatment options
High grade serous carcinoma and high-grade endometrioid carcinoma	Can present with peritoneal carcinomatosis, ascites, pelvic mass Typically advanced stage at presentation	Deficiencies in homologous recombination (50% of tumours) Associated with <i>BRCA</i> and <i>TP53</i> mutations	Platinum-based chemotherapy and PARP inhibitors Tumours are initially sensitive to platinum-based chemotherapy but most patients with advanced-stage cancer will recur .
Low-grade serous carcinoma	Presents in younger patients (median reported age 43-55 years (95)) Can be early or late stage at presentation	Associated with <i>KRAS</i> and <i>BRAF</i> mutations Tumours have genomic stability	MEK inhibitors and hormonal therapies
Low-grade endometrioid carcinoma	Can be associated with endometriosis	Associated with <i>PTEN</i> , <i>ARID1A</i> , <i>PIK3CA</i> mutations. Can have microsatellite instability	Possible hormonal therapies (not yet established)
Clear cell carcinoma	Can present with parenchymal metastases (in liver and lung) Can also be associated with hypercoagulability and hypercalcaemia.	Associated with <i>ARID1A</i> and <i>PIK3CA</i> mutations	Immunotherapy agents. Can be resistant to platinum-based chemotherapy.
Mucinous carcinoma	Presents in younger patients and is typically early stage at presentation.	Associated with <i>KRAS</i> mutations	Tends to be chemotherapy-insensitive but are still treated initially with cytotoxic chemotherapy.

MEK, mitogen-activated protein kinase kinase; PARP, poly (ADP ribose) polymerase.

Table 2. Functions of commonly mutated inherited genes associated with increased risk of ovarian cancer^{18, 22-25}

Gene	Protein	Protein function
<i>BRCA1</i>	Breast cancer type 1 susceptibility protein	Critically involved in the repair of double strand breaks by homologous recombination Serves as scaffold for other proteins involved in double strand DNA repair mostly through homologous recombination deficiency BRCA2 stabilizes RAD51-ssDNA complexes
<i>BRCA2</i>	Breast cancer type 2 susceptibility protein	
<i>BARD1</i>	BRCA1-associated RING domain protein 1	Forms a heterodimer with BRCA1 This complex is essential for mutual stability
<i>BRIP1</i>	Fanconi anemia group J protein	Binds to BRCA1 BRCA1-BRIP1complex is required for S-phase checkpoint activation
<i>PALB2</i>	Partner and localizer of BRCA2	Bridging protein that connects BRCA1 and BRCA2 at sites of DNA damage Helps load RAD51 onto ssDNA
<i>RAD51C</i>	DNA repair protein RAD51 homolog 3	Strand exchange proteins that bind to ssDNA breaks to form nucleoprotein filaments and initiate DNA repair
<i>RAD51D</i>	DNA repair protein RAD51 homolog 4	
<i>MSH2</i>	DNA mismatch repair protein Msh2	Mismatch repair proteins that recognize and repair basepairing errors occurring during DNA replication Mutations in mismatch repair genes are associated with Lynch syndrome
<i>MLH1</i>	DNA mismatch repair protein Mlh1	
<i>MSH6</i>	DNA mismatch repair protein Msh6	
<i>PMS2</i>	Mismatch repair endonuclease PMS2	
ssDNA, single-stranded DNA.		

Table 3. Staging of ovarian cancer

FIGO stage	Description	Corresponding TNM stage
Stage I: Tumor confined to ovaries or fallopian tube(s)		T1
IA	Tumor limited to one ovary (with ovarian capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1a
IB	Tumor limited to both ovaries (with ovarian capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1b
IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following C substages:	T1c
	IC1: Surgical spill	
	IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface	
	IC3: Malignant cells in the ascites or peritoneal washings	
Stage II: Tumor involves one or both ovaries, or the fallopian tubes with pelvic extension below the pelvic brim or primary peritoneal cancer (Tp)		T2
IIA	Extension and/or implant of tumour on uterus and/or fallopian tubes and/or ovaries	T2a
IIB	Extension of tumour to other pelvic intraperitoneal tissues	T2b
Stage III: Tumor involves one or both ovaries, or the fallopian tubes, or primary peritoneal cancer with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes		T3
IIIA	IIIA1: Positive retroperitoneal lymph nodes only (pathologically proven): IIIA1(i) Metastasis up to 10 mm in greatest dimension. IIIA1(ii) Metastasis >10 mm in greatest dimension. IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes.	T1, T2, T3aN1
IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b/T3b/N1
IIIC	Macroscopic peritoneal metastasis beyond the pelvis > 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)	T3c/T3cN1
Stage IV: Distant metastasis excluding peritoneal metastases		
IVA	Pleural effusion with positive cytology.	Any T, any N or M1
IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	Any T, any N or M1

Adapted from (127). FIGO, The International Federation of Gynecology and Obstetrics; TNM, TNM Classification of Malignant Tumours.

Table 4. Key clinical trials in newly diagnosed ovarian cancer

Study	Arms	Comments	Ref
Adjuvant therapy			
GOG 111	IV cisplatin and cyclophosphamide IV cisplatin and paclitaxel	Increase in PFS and overall survival with cisplatin/paclitaxel treatment.	8
AGO OVAR 3	IV cisplatin and paclitaxel IV carboplatin and paclitaxel	No significant difference between PFS or overall survival between treatment arms	10
GOG 158	IV cisplatin and paclitaxel IV carboplatin and paclitaxel	Carboplatin and paclitaxel were not inferior to cisplatin and paclitaxel	11
GOG 182	IV carboplatin and paclitaxel Other platinum based doublets	No significant difference between PFS or overall survival between treatment arms	9
SCOTROC	IV carboplatin and paclitaxel IV carboplatin and docetaxel	Similar PFS between study arms Less neuropathy observed with carboplatin and docetaxel treatment than with carboplatin and paclitaxel	12
GOG 172	IV cisplatin and paclitaxel IP cisplatin and paclitaxel and IV paclitaxel	Increase in PFS and overall survival with IP treatment compared with IV treatment	143
JGOG 3016	IV carboplatin and paclitaxel every 21 days IV carboplatin every 21 days and paclitaxel weekly (dose dense regimen)	Significant improvement in PFS and overall survival with dose dense therapy in patients with sub-optimally cytoreduced cancer. No difference in patients with optimally cytoreduced cancer	144, 145
GOG 252	IP cisplatin, IV and IP paclitaxel and bevacizumab IP carboplatin, IV weekly paclitaxel and bevacizumab IV carboplatin, IV weekly paclitaxel and bevacizumab	No difference in PFS between study arms Higher rates of hypertension, nausea and vomiting in IP cisplatin group	147
MITO-7	Weekly carboplatin and weekly paclitaxel Carboplatin and paclitaxel every 3 weeks	No difference in PFS or overall survival	149
MITO-2	Carboplatin and paclitaxel Carboplatin and pegylated liposomal doxorubicin	No difference in PFS or overall survival	150
Neoadjuvant therapy			

EORTC	Upfront surgery followed by chemotherapy	NACT followed by surgical cytoreduction was not inferior to surgical cytoreduction followed by adjuvant chemotherapy	160
	NACT, interval cytoreductive surgery, followed by completion of chemotherapy		
Kehoe et al	Upfront surgery followed by chemotherapy	NACT followed by surgical cytoreduction was not inferior to surgical cytoreduction followed by adjuvant chemotherapy	161
	NACT, interval cytoreductive surgery, followed by completion		
Maintenance therapy			
GOG 218	Carboplatin, paclitaxel and bevacizumab with bevacizumab maintenance	Increase in PFS with the addition of bevacizumab	151
	Carboplatin, paclitaxel and bevacizumab with placebo maintenance		
	Carboplatin, paclitaxel and placebo with placebo maintenance		
ICON7	Carboplatin, paclitaxel and bevacizumab with bevacizumab maintenance	Increase in PFS with the addition of bevacizumab	152
	Carboplatin and paclitaxel		
GOG262	IV carboplatin and paclitaxel every 21 days with or without bevacizumab	No difference in PFS in intent to treat patients between dose dense and 21-day dosing	148
	IV carboplatin every 21 days and IV weekly paclitaxel with or without dose-dense bevacizumab	Increase in PFS in patients receiving dose-dense treatment versus those receiving dosing every 21 days who were not given bevacizumab No difference in PFS in patients not receiving bevacizumab	
NCT00866697	Platinum-based chemotherapy and taxane maintenance therapy	Improved PFS with the addition of pazopanib No difference in overall survival between groups	156
	Platinum-based chemotherapy and taxane maintenance therapy with pazopanib		
AGO-OVAR 12	Carboplatin and paclitaxel	Improved PFS, but more gastrointestinal toxicities, with nintedanib.	154
	Carboplatin and paclitaxel with nintedanib		

NCT01493505	Carboplatin and paclitaxel	Results pending	155
	Carboplatin and paclitaxel with trebananib		

IP intraperitoneal; IV intravenous; NACT, neoadjuvant chemotherapy; PFS progression-free survival

Table 5. Key trials for treatment of recurrent ovarian cancer.

Study	Arms	Comments	Ref
Platinum-sensitive disease			
ICON4/AGO-OVAR-2.2	Carboplatin	Increase in PFS and overall survival with the addition of paclitaxel	180
	Carboplatin and paclitaxel		
OCEANS	Carboplatin, gemcitabine and bevacizumab with bevacizumab maintenance therapy	Increase in PFS with the addition of bevacizumab	184
	Carboplatin and gemcitabine		
ICON6	Platinum-based chemotherapy and cediranib with cediranib maintenance therapy	Significant improvement in PFS Overall survival results are pending	185
	Platinum-based chemotherapy		
NOVA	Platinum-based chemotherapy for platinum-sensitive recurrence followed by maintenance niraparib	Significant improvement in PFS (in women with germline BRCA mutations or homologous recombination deficiency) group for niraparib versus placebo	Ref: www.Tesarobio.com press release June 28, 2016 and ESMO 2016 Oct
	Platinum-based chemotherapy for platinum-sensitive recurrence, followed by maintenance with placebo drug		
NCT00113607	Pegylated liposomal doxorubicin and trabectedin	Significant increase in PFS with the addition of trabectedin	186
	Pegylated liposomal doxorubicin		
NCT00753545	Platinum-based chemotherapy with or without olaparib maintenance therapy	Significant increase in PFS with olaparib maintenance therapy	200

NCT01081951	Carboplatin and paclitaxel with or without olaparib maintenance therapy	Increase in PFS with olaparib maintenance therapy	201
Platinum-resistant disease			
AURELIA	Paclitaxel with or without bevacizumab	Increased PFS and response rate with the addition of bevacizumab. Paclitaxel + bevacizumab was the best combination – increased response rate, PFS and overall survival.	187, 188
	Pegylated liposomal doxorubicin with or without bevacizumab		
	Topotecan with or without bevacizumab		

PFS, progression-free survival.

Table 6. Ongoing clinical trials for treatment of ovarian cancer

Type of biologic therapy	Example	Target	Comments	Ref
Anti-angiogenics	Bevacizumab Cediranib	VEGF VEGFR1, 2, 3	Single agent activity in both platinum-resistant and platinum-sensitive cancer	184, 185, 187-194
PARP inhibitors	Olaparib	PARP	Olaparib approved by the EMA for treatment of platinum-sensitive recurrent cancer as a maintenance therapy and by the FDA for recurrent ovarian cancer in women with germline <i>BRCA</i> mutations and who have received at least 3 prior lines of chemotherapy	193-202, 204-208, 245
	Rucaparib		Results pending	
	Veliparib		Results pending	
Immunotherapies	Nivolumab	Programmed cell death protein-1	15% response rate and 50% disease control rate	214
	Pembrolizumab	Programmed cell death protein-1	11.5% response rate and 23.1% of patients had stable disease	215

	Avelumab	Programmed cell death 1 ligand 1	10.7% risk reduction and 54.7% disease control rate. 2 patients with a clear cell histology showed evidence of an objective response rate.	216
	Ipilimumab	Cytotoxic T-lymphocyte protein 4	Results pending	217, 218
Antibody–drug conjugate	IMGN853	Folate receptor α	Promising preliminary data	219
Combination	Cediranib and olaparib	Various	Increased PFS in patients that received cediranib/olaparib, compared with patients receiving olaparib alone. Currently being tested in phase III studies in both platinum-resistant as well as platinum-sensitive recurrent cancer	193, 194, 238
	Pembrolizumab and niraparib		Results pending	240
	BKM120 or BYL719 and olaparib		Maximum tolerated dose achieved for BKM120 and olaparib; anti-cancer activity noted for this combination	239

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